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09/833,526	04/11/2001	David A. Horwitz	A-68983-1/RFT/RMS/RMK	2496

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/833,526	Applicant(s) HORWITZ, DAVID A.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 2 and 4-7 are pending.

2. The reference B2 on PTO 1449 filed 6/25/02 has been crossed out because said reference has been cited in previous Office Action.

3. Claims 4 and 7 are objected to because they depend on canceled claim 1.

4. The following new grounds of rejections are necessitated by the amendment filed 6/7/02.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. An inadvertent typographical error for WO 99/45524 (Sept 1999; PTO 892) in the previous Office Action has been noted; the corrected publication should have been WO 99/48524.

7. Claims 2, 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Garderet et al (Transplantation 67(1): 124-30; Jan 1999; PTO 892).

The WO 99/48524 publication teaches a method to decrease graft rejection by inducing T cell tolerance *ex vivo*. The reference method comprises isolating peripheral mononuclear blood cells (PMBCs) from a donor and a recipient, mixing irradiated donor and recipient PMBCs ex vivo (See page 18, lines 10-16, See claims of WO99/48524, in particular), treating the reference PMBCs with a regulatory composition such as TGF-β (See page 7, line 1-2, page 13, line 8-9, page 14, line 2-7, in particular). After expanding said cells in culture, the reference cells are transferred to the recipient (See page 24, lines 1-3, see claim 5 of WO99/48524, in particular). The reference method further enriched for CD8+ T cells (See page 12, lines 22-23, in particular).

The WO 99/48524 publication teaches the method for inducing T cell tolerance is useful for suppressing Graft versus Host Disease (GVHD) in patients (See Abstract, in particular).

The claimed invention as recited in claim 2 differs from the reference only by the recitation that the method for inducing a recipient's cells to decrease graft rejection comprising treating said PBVC cells with a regulatory composition comprising TGF-β and irradiated T cell-depleted mononuclear cells from donor.

Garderet *et al* teach a method of depleting alloreactive lymphocytes of donor from peripheral blood mononuclear cell preparation to reduce graft versus host disease (graft rejection). The reference method comprises treating PMBC cells with irradiated peripheral blood mononuclear cell from recipient and expand said cell in culture (See abstract, in particular). The reference further teaches selective enrichment of CD4+ T cells and depletion of host specific alloreactive CD4+ T cell. The advantage of the reference method inhibits host specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method for inducing a recipient's cells to decrease graft rejection by isolating PMBCs from recipient and donor and treating the PMBC ex vivo with TGFβ, expanding said PMBC cells following treatment and introducing said treated PMBC cells to the recipient as taught by the WO 99/48524 publication with the method of reducing graft rejection by treating PMBCs with irradiated T cell depleted mononuclear cell PMBC from donor as taught by Garderet *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Garderet *et al* teach coculturing irradiated T cell depleted monoclonal cells from donor and recipient inhibits host specific cytotoxic activity and allows therapeutic infusion (reconstitution) of T cells after allografts with a reduced capacity to produce graft-versus host disease (See Abstract, in particular). The WO 99/48524 publication teaches the method for inducing T cell tolerance is useful for suppressing Graft versus Host Disease (GVHD) in patients (See Abstract, in particular).

8. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Garderet *et al* (Transplantation 67(1): 124-30; Jan 1999; PTO 892) as applied to claims 2, 5 and 7 and further in view of Bonig *et al* (of record, Scand J Immunol 50: 612-618, Dec 1999; PTO 892) or Dooms *et al* (Abstract, European Cytokine Network 9(3): 169; 1998; PTO 1449).

The teachings of WO 99/48524 publication and Garderet *et al* have been discussed supra.

The claimed invention as recited in claim 4 differs from the references only by the recitation that the method for inducing a recipient's cells to decrease graft rejection further comprises cytokine selected from the group consisting of IL-2 and IL-15.

Bonig *et al* teach IL-15 has some functional similarities to IL-2 since they share a common signal transduction pathway (See page 612, column 1, first paragraph, in particular) and addition of TGF-β, which is a potent suppressor of T cell proliferation, to T cell culture in vitro in the presence of IL-15 or IL-2 further inhibits IFNγ production mediated by either IL-15 or IL-2 alone (See page 615, Figs 2C and 2E, Fig 3, Table 1, in particular). Bonig *et al* further teach that addition of TGF-β to IL-2 or IL-15 culture reduces the number of IFN-γ/CD4 +/+ and IFN-γ/CD8 +/+ cells by 50% and reduces cytoplasmic interferon-accumulation equally in CD4+ and CD8+ cells (See Table 1, in particular).

Dooms *et al* teach IL-2 pretreatment sensitizes T cells for Fas/Apo-1 apoptosis whereas IL-15 pretreatment induces T cell anergy (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine IL-15 or IL-2 as taught by Bonig *et al* or Dooms *et al* with the TGF-β for a method of inducing T cell tolerance (anergy) ex vivo to decrease graft rejection as taught by the WO 99/48524 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to this because Bonig *et al* teach that a combination of TGF-β and IL-15 or IL-2 further reduces the number of IFN-γ/CD4 +/+ and IFN-γ/CD8 +/+ cells by 50% and reduces cytoplasmic interferon-accumulation equally in CD4+ and CD8+ cells (See Table 1, in particular) wherein said cells are responsible for T cell tolerance or the lack thereof such as anti-tumor activity. Dooms *et al* teach IL-2 pretreatment

sensitizes T cells for Fas/Apo-1 apoptosis whereas IL-15 pretreatment induces T cell anergy (See abstract, in particular).

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48524 publication (of record, Sept 1999, PTO 892) in view of Garderet *et al* (Transplantation 67(1): 124-30; Jan 1999; PTO 892) as applied to claims 2, 5 and 7 and further in view of Early *et al* (Clin Exp Immunol 116(3): 527-33, June 1999; PTO 892), Heitger *et al* (Blood 90(2): 850-57, July 1997; PTO 892) and Chen *et al* (J Immunology 161: 909-918, 1998; PTO 892).

The teachings of WO 99/48524 publication and Garderet *et al* have been discussed supra.

The claimed invention as recited in claim 6 differs from the references only by the recitation that the method for inducing a recipient's cells to decrease graft rejection wherein said CD4+ cells are enriched for naïve CD4+ T cells.

Early *et al* teach a method of enriching for naïve CD4+ T cells for reducing the incidence of graft versus host disease (See abstract, in particular). The reference shows that CD4+ CD45RA+ naïve T cells from human cord blood can transform more quickly than their adult counterpart into functionally equivalent CD4+CD45RO+ (memory) T cells.

Heitger *et al* teach CD45 isotype has been linked to different cell functions such as CD4+/CD45RA+ (naïve) T cells acting as suppressor/inducer cells whereas CD4+/CD45RO+ (memory) T cells acting as helper/inducer cells (See page 850, column 1, in particular).

Chen *et al* teach CD45 specific T cell plays a role in graft versus host disease (See entire document, page 912, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to enrich CD4+ CD45RA+ naïve T cells as taught by Early *et al*, Heitger *et al* and Chen *et al* to decrease graft rejection by treating said cells ex vivo with TGFβ as taught by the WO 99/48524 publication and irradiated T cell depleted mononuclear cell PMBC from donor as taught by Garderet *et al* for a method of decreasing graft rejection as taught by the WO 99/48524 publication and Garderet *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Chen *et al* teach CD45 specific T cell plays a role in graft versus host disease (See entire document, page 912, column 1, in particular). Heitger *et al* teach CD45

isotype has been linked to different cell functions such as CD4+/CD45RA+ (naïve) T cells acting as suppressor/inducer cells whereas CD4+/CD45RO+ (memory) T cells acting as helper/inducer cells (See page 850, column 1, in particular). Early *et al* teach enriching for naïve CD4+ T cells could reducing the incidence of graft versus host disease (See abstract, in particular).

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.

Patent Examiner .

Technology Center 1600

August 26, 2002

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